NOVEL CLINICAL INDICATIONS FOR DIGITAL VARIANCE ANGIOGRAPHY (DVA) AND THE CLINICAL USABILITY OF COLOR-CODED DVA

PhD thesis

István Góg

Doctoral College of Semmelweis University

Cardiovascular Medicine and Research Division

Supervisor: Péter Sótonyi, MD, D.Sc

Official reviewers: Arnold Tóth, MD, Ph.D
Miklós Vértes MD, Ph.D

Members of the Complex Examination Committee:

György Wéber, MD, D.Sc
Pál Ákos Deák, MD, Ph.D
Rudolf Ménesi, MD, Ph.D

Budapest

2025

INTRODUCTION

The gold standard algorithm in the last 40 years was digital subtraction angiography (DSA), which was described in 1935. The method is based on the subtraction of a mask image from the post-injection image series. This subtracted sequence can be further processed into a stacked opacification image, which can be used as a roadmap during vascular intervention. The mask image can also be post-processed to eliminate noise originating from patient movement.

DVA is a novel method developed by Szigeti and Osváth that claimed to be able to produce an angiographic image very similar to DSA. In 2018, the results of a retrospective study published by Gyánó et al. showed that a previously measured signal-to-noise ratio benefit of DVA is also observable in a clinical setting. In the following years, other retrospective studies aimed at comparing DSA and DVA resulted in similar results. To provide evidence of hypothesized dose management capabilities, Óriás et al. studied the effects of 50% contrast media dose reduction while using DVA and their work revealed a significant advantage over standard-dose DSA. The radiation dose-reducing potential of DVA was studied in 2021 by Gyánó et al. in a prospective study involving 30 patients and visual

comparison validated a non-inferiority of reduced-dose DVA images to standard-dose DSA images. A randomised controlled trial that enrolled 114 patients revealed an achievable DSA-related radiation dose reduction of 61% with the use of DVA without compromising diagnostic image quality.

It is well known that DSA provides a two-dimensional image, which often gives inadequate information. If functional data could be acquired, decision-making would be much easier in difficult instances. Converting conventional greyscale DSA images into color-coded representations to provide a better understanding of vascular dynamics is called parametric or color-coded angiography. The most important parameter is Time to Peak (TTP), which is basically the time for the contrast intensity to reach its maximum value. All major manufacturers developed its own color-coded imaging technology, but the most known is Siemens' Syngo iFlow. Besides several potential clinical use, color-coded angiography has several limitations, including the higher radiation dose requirements. DVA can also be combined with color-coding, which seems promising, as DVA may have the potential to counter the mentioned radiation dose related limitation.

OBJECTIVES

1. The advantages of DVA were proved in lower limb interventions. **Can DVA be used in other therapeutic indications?**

The aim is to assess the potential advantages of DVA in TACE and PAE procedures.

2. **What are the qualitative advantages of color-coded DVA in other therapeutic indications?**

The aim is to evaluate the potential benefits of ccDVA in PAE.

3. **Is the DVA-based color-coded imaging is a reliable tool for the measurement of time-related parameters?**

The aim is to compare the calculated parameters of ccDVA with Syngo iFlow, a commercially available parametric angiographic method.

Three different smaller-scale retrospective proof-of-concept studies were conducted to complete these objectives (see Bibliography).

MATERIALS AND METHODS

Twenty-five patients with hepatocarcinoma underwent transarterial chemoembolization (TACE) in. Pre-embolisation angiographies were retrospectively acquired, and DSA and DVA images were generated with separate workstations.

Thirty male patients underwent prostatic artery embolisaton (PAE) between May and October 2020 who previously did not receive TURP treatment for prostate hyperplasia. The images were extracted from the angiographic workstations as unsubtracted image series, which were used for DSA and DVA image generation. In both embolization studies, contrast-to-noise (CNR) measurements were performed and expert interventional radiologists also performed single-image and paired visual evaluations.

In 2020, 19 patients with PAD underwent peripheral intervention. Image data were used in a retrospective, observational investigation to study colour-coded DVA and compare it with Siemens Syngo iFlow technology.

Both technologies allowed the selection of optionally sized ROIs, in which, the measurement of time-to-peak (TTP) parameter was performed in identical positions.

RESULTS

TACE study

From the image data of twenty-five patients (65% male, mean ± SD age: 67.5 ± 11.2 years), fifty DSA and DVA image pairs were created. For CNR measurements a total of 686 ROI pairs were selected on both image types. The median of DSA CNR was 13.34 (IQR: 9.21), whereas DVA measurements resulted in a 16.02 median value (IQR: 14.89), and the derived ratio of CNR pairs was 1.24 (median, IQR: 0.69). According to Wilcoxon's signed-rank test, this difference was significant ($p<0.05$)

The visual survey, which involved the single image evaluation of 50 DSA and 50 DVA images, resulted in a median Likert score of 3.0 (IQR: 1.2) for DSA and 3.34 (IQR: 0.55) for DVA. The difference was significant according to the Wilcoxon signed-rank test ($p<0.001$). Kendall's W test was also performed to assess interrater agreement. In the case of DSA-related answers, the agreement was strong (W: 0.610, $p<0.001$), and in the case of DVA, the agreement was moderate but still significant (W: 0.423, $p<0.001$).

The survey focusing on diagnostic abilities determined that readers failed to visualise feeding arteries and lesions in only 8% of DVA images, whereas in the case of DSA, 28% of images

were not able to visualise lesions. This difference was significant according to the two-sided Z-test ($p > 0.01$). The results for the question regarding feeding artery detection were 16% (DVA) and 32% (DSA) failure of detection. A two-sided Z-test verified a significant difference ($p<0.05$) in this case also. The inter-rater agreement evaluation indicated moderate agreement for both questions. For feeding artery detection, Kendall's W for DSA was 0.541 ($p<0.001$), and for DVA was 0.551 ($p<0.001$), and for lesion detection, the W of DSA was 0.564 ($p<0.001$), and that of DVA was 0.561 ($p<0.001$). Regarding image type preference, in 80% of the responses, DVA was preferred. Two representative DSA and DVA image pairs are shown in Figure 1.

PAE study

CNR measurements were performed on 108 DSA and DVA image pairs created from image data of 30 male patients (aged 68.0 ± 8.9 years). CNR samples were taken from a total of 1418 locations (ROI pairs). The median DSA CNR was 7.33 (IQR: 6.40) and 29.99 (IQR: 25.93) for DVA. The median R-value (DVA CNR divided by the corresponding DSA CNR) was 4.11 (IQR: 1.72). The Wilcoxon signed-rank test verified a significant increase in the CNR provided by DVA ($p < 0.001$).

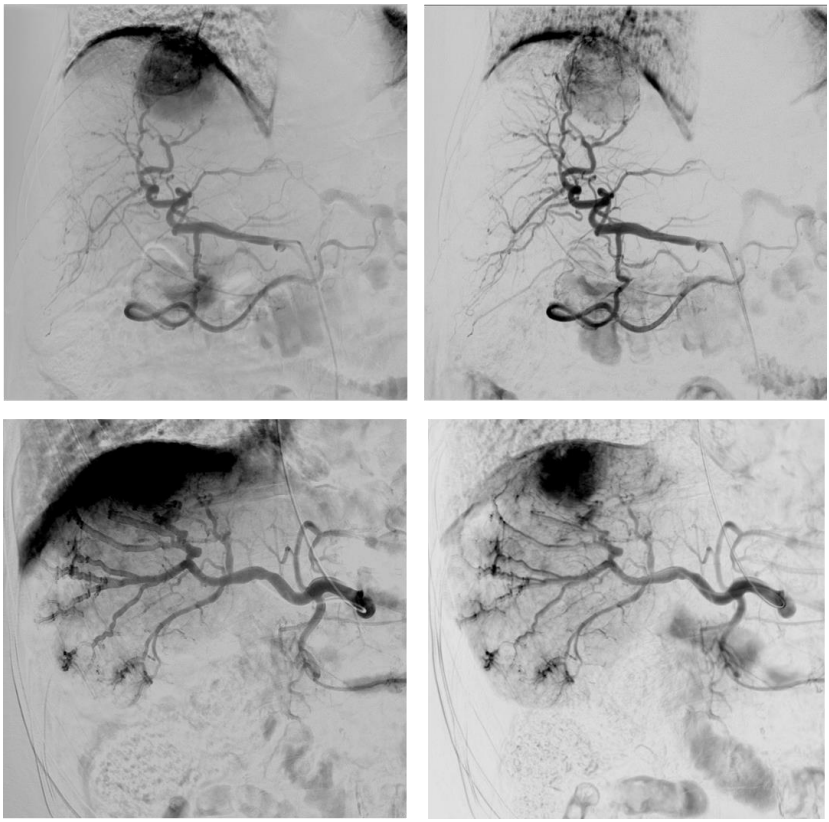

Figure 1. Comparison of a representative DSA (left panels) and DVA (right panels) image pairs. The DSA and DVA images were generated from the same unsubtracted image series using the Siemens Syngo or the Kinepict Medical Imaging Tool software, respectively.

Single-image assessment of 108 DSA and 108 DVA images was perfomed in a similar way as in PAE study. DVA images' median score reached 4.50 (IQR 0.75), while DSA images received 3.39 (median IQR: 1.00), which was significantly

lower, according to Wilcoxon's signed rank test ($p < 0.001$). The inter-rater agreement was high in both groups (87% for DSA and 92% for DVA), which was determined to be significant, although moderate agreement was observed by Kendall's W test (DVA W = 0.38, DSA W = 0.53).

The second part of the visual evaluation (paired comparison) showed a significantly higher preference for color-coded DVA images over DSA in all evaluated categories (visibility of large vessels, small vessels, feeding artery, and tissue blush) according to the binomial test ($p<0.01$). This meant an 89% preference for DVA for tissue blush visibility, 79% for small vessel visibility, 79% for feeding artery visibility, and 63% for large vessel visibility. The inter-rater agreement was between 58% and 79%, which was slight but significant in the three categories according to Fleiss' kappa test. For large vessels, agreement was not statistically significant. Results are shown in To illustrate the differences of DSA and ccDVA, an example is shown in Figure 2.

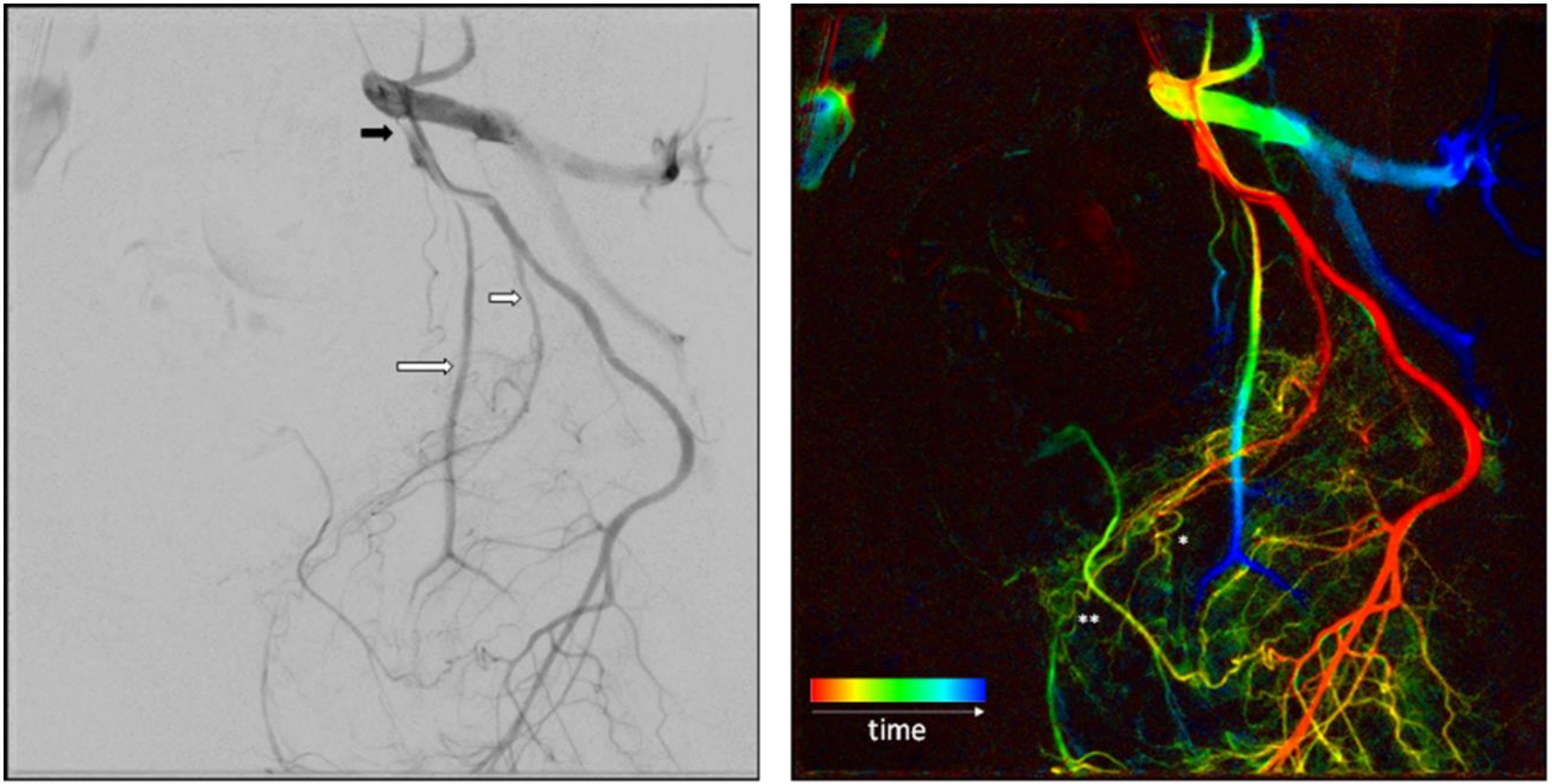

Figure 2. Representative example of digital subtraction angiography (DSA) and color-coded digital variance angiography (ccDVA) images in a 63 year-old patient. Left: Application of 6 ml contrast agent (3 ml Vispaque 320 and 3 ml NaCl 0.9% solution) in the left pudendal artery (PuA) at the origin from the distal internal iliac artery (black arrow). The prostatic artery (short white arrow) is visible as a direct branch from the PuA. Proximal of the origin of the PuA the inferior vesical artery (IVA) is visible (long white arrow), with a proximal smaller lumen, suspicious for a stenosis. Right: The colors represent the time elapsed until the appearance of the contrast media in a specific blood vessel segment. In the IVA, color progression from orange to blue is visible, indicating a slower flow. Smaller vessels, like the characteristic corkscrew pattern (*) or the collateralization of dominant prostatic artery to the pudendal areas (**) have a higher visibility, and parenchymal blush is visible as greenish diffuse attenuation.

CcDVA study

A total of twenty-two pre- and post-interventional color-coded DSA images and the same number of color-coded DVA images were created in a previously detailed process. The data were divided by acquisition rates, resulting in the "4 FPS" and the "7.5 FPS" groups. Total procedural contrast agent dose per patient was 69,9 (+- 35,2) ml (mean +- SD).

The analysis of 22 pre- and post-angioplasty image pairs resulted in the selection of 53 pre- and post-angioplasty ROI pairs in the "4 FPS" group and 32 pairs in the "7,5 FPS" group. When we compared the change in passage time, only those image pairs were used, where four ROIs were present for the reason that this way, the data collection seemed more homogenous, as in cases where only three ROIs per image were selected, the distance from the site of treatment varied highly.

In the analysis of the relationship between the TTP parameter and different imaging protocols, the correlation was found to be very high regardless of the acquisition settings. Pearson's r value was 0.99 ($p<0.0001$) and R^2 was 0.98 in both FPS groups. For visual representation, see Figure 3.

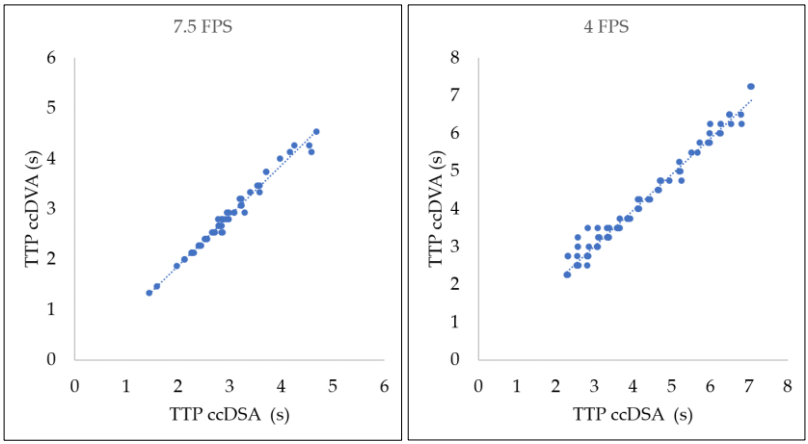

Figure 3. Correlation of TTP values calculated by ccDSA and ccDVA in different acquisition protocols. Right panel: correlation of 106 ROI pairs in 4 FPS acquisitions. Left panel: correlation of 64 ROI pairs in 7.5 FPS acquisitions.

To investigate the relationship between different ROI positions and TTP parameters, a similar correlation testing was performed, and the resulting r and R^2 values showed a very high correlation ($r = 0.99$, $p < 0.0001$, $R^2 = 0.98$) in all ROI positions (not shown).

The change in passage time was also calculated, as we hypothesised that it could represent the change in haemodynamic conditions in the surveyed area. This passage time was obtained by subtracting the TTP measured in the 1st ROI from the TTP of the 4th ROI. Change in passage time was

obtained by subtracting post-interventional passage time from pre-interventional passage time. Correlation analysis showed that this parameter was measured likewise by both imaging software ($r = 0.98$, $p < 0.0001$, $R^2 = 0.96$).

Results regarding change of passage time comparison is show in Figure 4.

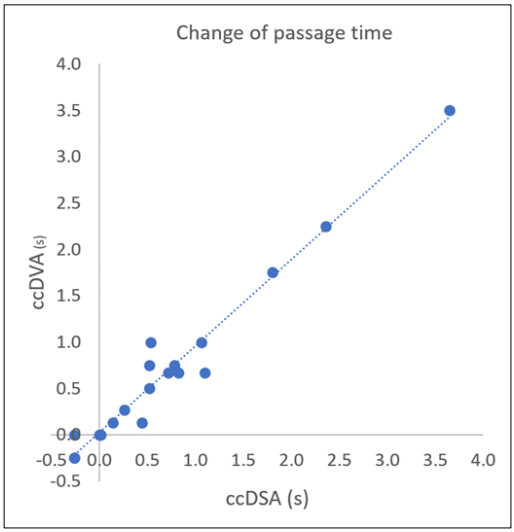

Figure 4. Correlation of the change passage time calculated from TTP data of ccDSA and ccDVA. We could not place the 4th ROI in 3 interventions. Therefore, only 19 ROI pairs were used in the analysis. The change of passage time was calculated as the difference of (TTPROI4-TTPROI1) before and after intervention.

CONCLUSIONS

1. By using contrast-to-noise measurements and visually comparing the quality and diagnostic value of DSA-DVA image pairs, we demonstrated that DVA has superior image quality and diagnostic value in PAE and liver TACE procedures. Thereby, we provided evidence that the advantages of DVA can be observed in abdominal and pelvic interventions.

2. By visually comparing DSA and ccDVA, we have found evidence that ccDVA has the potential to augment PAE interventions by delivering more detailed information on small arteries, feeding arteries and tissue blush. All these structures are critically important in the embolization procedure, therefore their better visibility might improve the safety and efficacy of PAE interventions.

3. By measuring and comparing time-to-peak values of paired ccDVA and iFlow images, we demonstrated the equivalence between the two parametric angiographic method regarding TTP measurement, which suggests DVA's utility as an alternative decision-support tool in endovascular interventions. The lower radiation load required by DVA technology might help to increase the use and significance of color-coded parametric imaging in minimally invasive endovascular interventions.

BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

Publications that are the subject of the doctoral thesis:

Alizadeh LS, Gyánó M, **Góg I**, Szigeti K, Osváth S, Kiss JP, Yel I, Koch V, Grünewald LD, Vogl TJ, Booz C. Initial Experience Using Digital Variance Angiography in Context of Prostatic Artery Embolisation in Comparison with Digital Subtraction Angiography. Acad Radiol. 2023 Apr 1;30(4):689–97.

Lucatelli P, Rocco B, Ciaglia S, Teodoli L, Argirò R, Guiu B, Saba L, Vallati G, Spiliopoulos S, Patrone L, Gyánó M, **Góg I,** Osváth S, Szigeti K, Kiss JP, Catalano C. Possible use of Digital Variance Angiography in Liver Transarterial Chemoembolisation: A Retrospective Observational Study. Cardiovasc Intervent Radiol. 2023 Apr 19;46(5):635–42.

Góg I, Sótonyi P, Nemes B, Kiss JP, Szigeti K, Osváth S, Gyánó M. Quantitative Comparison of Color-Coded Parametric Imaging Technologies Based on Digital Subtraction and Digital Variance Angiography: A Retrospective Observational Study. J Imaging. 2024 Oct 18.

Other publications related to the topics mentioned in this thesis

Gyánó M, **Góg I**, Óriás VI, Ruzsa Z, Nemes B, Csobay-Novák C, Oláh Z, Nagy Z, Merkely B, Szigeti K, Osváth S, Sótonyi P. Kinetic Imaging in Lower Extremity Arteriography: Comparison to Digital Subtraction Angiography. Radiology. 2018 Oct 16;290(1):246–53.

Óriás VI, Gyánó M, **Góg I**, Szöllősi D, Veres DS, Nagy Z, Csobay-Novák C, Zoltán O, Kiss JP, Osváth S, Szigeti K, Zoltán R, Sótonyi P. Digital Variance Angiography as a Paradigm Shift in Carbon Dioxide Angiography. Invest Radiol. 2019 Mar 1;54(7):428–36.

Gyánó M, Csobay-Novák C, Berczeli M, **Góg I**, Kiss JP, Szigeti K, Osváth S, Nemes B. Initial Operating Room Experience with Digital Variance Angiography in Carbon Dioxide-Assisted Lower Limb Interventions: A Pilot Study. Cardiovasc Intervent Radiol. 2020 May 31;43(8):1226–31.

Bastian MB, König AM, Viniol S, Gyánó M, Szöllősi D, **Góg I**, Kiss JP, Osvath S, Szigeti K, Mahnken AH, Thomas RP. Digital Variance Angiography in Lower-Limb Angiography with Metal Implants. Cardiovasc Intervent Radiol. 2020 Nov 3;44(3):452–9.

Gyánó M, Berczeli M, Csobay-Novák C, Szöllősi D, Óriás VI, **Góg I**, Kiss JP, Veres DS, Szigeti K, Osváth S, Pataki Á, Juhász V, Oláh Z, Sótonyi P, Nemes B. Digital variance angiography allows about 70% decrease of DSA-related radiation exposure in lower limb X-ray angiography. Sci Rep. 2021 Nov 8;11(1).

Thomas RP, Bastian MB, Viniol S, König AM, Amin SS, Eldergash O, Schnabel J, Gyánó M, Szöllősi D, **Góg I**, Kiss JP, Osváth S, Szigeti KP, Mahnken AH. Digital Variance Angiography in Selective Lower Limb Interventions. J Vasc Interv Radiol. 2021 Oct 13;33(2):104–12.

Sótonyi P, Berczeli M, Gyánó M, Legeza P, Mihály Z, Csobay-Novák C, Pataki Á, Juhász V, **Góg I**, Szigeti K, Osváth S, Kiss JP, Nemes B. Radiation Exposure Reduction by Digital Variance Angiography in Lower Limb Angiography: A Randomized Controlled Trial. J Cardiovasc Dev Dis. 2023 Apr 30;10(5):198.

Góg I, Sótonyi P, Kiss JP, Szigeti K. Application of Color-coded Digital Variance Angiography in Endovascular Interventions. Scientia et Securitas. 2024 Aug 5;4(4):240–248

∑IF: 38,221